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NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	JUL 02	LMEDLINE coverage updated
NEWS 3	JUL 02	SCISEARCH enhanced with complete author names
NEWS 4	JUL 02	CHEMCATS accession numbers revised
NEWS 5	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 6	JUL 16	CAplus enhanced with French and German abstracts
NEWS 7	JUL 18	CA/CAplus patent coverage enhanced
NEWS 8	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 9	JUL 30	USGENE now available on STN
NEWS 10	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS 11	AUG 06	FSTA enhanced with new thesaurus edition
NEWS 12	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS 13	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 14	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS 15	AUG 27	USPATOLD now available on STN
NEWS 16	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data
NEWS 17	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS 18	SEP 13	FORIS renamed to SOFIS
NEWS 19	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS 20	SEP 17	CA/CAplus enhanced with printed CA page images from 1967-1998
NEWS 21	SEP 17	CAplus coverage extended to include traditional medicine patents
NEWS 22	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS 23	OCT 02	CA/CAplus enhanced with pre-1907 records from Chemisches Zentralblatt
NEWS 24	OCT 19	BEILSTEIN updated with new compounds
NEWS 25	NOV 15	Derwent Indian patent publication number format enhanced
NEWS 26	NOV 19	WPIX enhanced with XML display format

NEWS EXPRESS 19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that

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specific topic.

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FILE 'HOME' ENTERED AT 20:23:12 ON 21 NOV 2007

=> file hcaplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'HCAPLUS' ENTERED AT 20:23:21 ON 21 NOV 2007
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FILE COVERS 1907 - 21 Nov 2007 VOL 147 ISS 22
FILE LAST UPDATED: 20 Nov 2007 (20071120/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s serine () kinase?
        116714 SERINE
          1893 SERINES
        117434 SERINE
                  (SERINE OR SERINES)
        314708 KINASE?
L1         750 SERINE (W) KINASE?

=> s l1 and isoform?
         85984 ISOFORM?
L2          54 L1 AND ISOFORM?

=> s l2 and inhibitor?
       1070314 INHIBITOR?
L3          25 L2 AND INHIBITOR?

=> s l3 and ovarian () cancer?
         72311 OVARIAN
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            2 OVARIANS
        72312 OVARIAN
                (OVARIAN OR OVARIANS)
       354501 CANCER?
        11627 OVARIAN (W) CANCER?
L4          1 L3 AND OVARIAN (W) CANCER?

=> d l4, ibib abs hitstr, 1

L4   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2007:117791  HCAPLUS
DOCUMENT NUMBER:          146:203915
TITLE:                    Gene expression profile for diagnosing small cell lung
                          cancer, discriminating from non-small cell lung
                          cancer, and assessing chemotherapy-resistant lung
                          cancer
INVENTOR(S):              Nakamura, Yusuke; Daigo, Yataro; Nakatsuru, Shuichi
PATENT ASSIGNEE(S):       Oncotherapy Science, Inc., Japan; The University of
                          Tokyo
SOURCE:                   PCT Int. Appl., 215pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2007013665         A2    20070201    WO 2006-JP315254        20060726
     WO 2007013665         A3    20070705
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
             KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN,
             MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU,
             SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG,
             US, UZ, VC, VN, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
PRIORITY APPLN. INFO.:                   US 2005-703192P     P  20050727
                                         US 2006-799961P     P  20060511
AB   Methods for detecting and diagnosing small cell lung cancer (SCLC) are
     described.  In one embodiment, the diagnostic method involves determining the
     expression level of an SCLC-associated gene that discriminates between SCLC
     cells and normal cells.  In another embodiment, the diagnostic method
     involves determining the expression level of an SCLC-associated gene that
     distinguishes two major histol. types of lung cancer, i.e., non-small cell
     lung cancer (NSCLC) and SCLC.  Finally, the present invention provides
     methods of screening for therapeutic agents useful in the treatment of
     small cell lung cancer, methods of treating small cell lung cancer, and
     methods for vaccinating a subject against small cell lung cancer.
     Furthermore, the present invention provides chemotherapy-resistant lung
     cancer- or SCLC-associated genes as diagnostic markers and/or mol. targets
     for therapeutic agent for these cancers.  These genes are up-regulated in
     chemoresistant lung cancer or SCLC.  Accordingly, chemoresistant lung
     cancer or SCLC can be predicted using expression level of the genes as
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diagnostic markers. As the result, any adverse effects caused by ineffective chemotherapy can be avoided, and more suitable and effective therapeutic strategy can be selected.

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     (FILE 'HOME' ENTERED AT 20:23:12 ON 21 NOV 2007)

     FILE 'HCAPLUS' ENTERED AT 20:23:21 ON 21 NOV 2007
L1           750 S SERINE () KINASE?
L2            54 S L1 AND ISOFORM?
L3            25 S L2 AND INHIBITOR?
L4             1 S L3 AND OVARIAN () CANCER?

=> s l1 and ovarian () cancer?
          72311 OVARIAN
              2 OVARIANS
          72312 OVARIAN
                    (OVARIAN OR OVARIANS)
         354501 CANCER?
          11627 OVARIAN (W) CANCER?
L5             1 L1 AND OVARIAN (W) CANCER?

=> s l1 and cancer?
         354501 CANCER?
L6            55 L1 AND CANCER?

=> s l6 and review/dt
        2088780 REVIEW/DT
L7             8 L6 AND REVIEW/DT

=> d l7, ibib abs hitstr, 1-8

L7   ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2007:160139  HCAPLUS
DOCUMENT NUMBER:          146:371632
TITLE:                    Malignant glioma drug discovery - targeting protein
                          kinases
AUTHOR(S):                Sathornsumetee, Sith; Vredenburgh, Kaitlyn A.;
                          Lattimore, Kathryn P.; Rich, Jeremy N.
CORPORATE SOURCE:         The Preston Robert Tisch Brain Tumor Center, Duke
                          University Medical Center, Durham, NC, 27710, USA
SOURCE:                   Expert Opinion on Drug Discovery (2007), 2(1), 1-17
                          CODEN: EODDBX; ISSN: 1746-0441
PUBLISHER:                Informa Healthcare
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review. Malignant gliomas are uncommon, but extremely lethal,
     cancers. Current standard-of-care includes surgery, radiation and
     chemotherapy, but recent research has generated a shift towards targeting
     the aberrant signal transduction components that underlie the pathogenesis
     of malignant gliomas. Protein kinases are a family of enzymes that are
     key elements in signal transduction-regulated cellular homeostasis
     subdivided based on their catalytic activity into tyrosine kinases and
     serine/threonine kinases. Protein kinases can be deregulated by several
     mechanisms, including genomic rearrangement, mutations of oncogenes or
     loss of tumor suppressor genes and overexpression or mutation of growth
     factor receptors to contribute to cancer initiation and
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maintenance. In malignant gliomas, several protein kinases are commonly over activated and may represent new therapeutic targets. Two main classes of agents targeting protein kinases are monoclonal antibodies and small-mol. inhibitors. In clin. trials, these molecularly targeted therapies have demonstrated limited efficacy as single agents in unselected malignant glioma patient populations. Several mechanisms of the failure of targeted agent monotherapies have been elucidated as new therapeutic strategies have emerged to overcome the resistance. Multi-targeted kinase inhibitors and combinations of single-targeted kinase inhibitors with one another or with traditional cytotoxics may increase treatment efficacy. Identification of biomarkers of response or resistance will be of paramount importance to enrich patients for specific targeted agents based on their genetic/mol. signature. In this review, the authors discuss the role of protein kinases in malignant glioma and how to target aberrant protein kinases with novel therapeutics.

REFERENCE COUNT: 149 THERE ARE 149 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:393473 HCAPLUS
DOCUMENT NUMBER: 145:305233
TITLE: Protein kinases and phosphatases as therapeutic targets in cancer
AUTHOR(S): Ventura, Juan-Jose; Nebreda, Angel R.
CORPORATE SOURCE: Spanish National Cancer Center (CNIO), Madrid, Spain
SOURCE: Clinical & Translational Oncology (2006), 8(3), 153-160
CODEN: CTOLAM; ISSN: 1699-048X
PUBLISHER: Instituto de Investigaciones Biomedicas CSIC/UAM
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Protein phosphorylation plays key roles in many physiol. processes and is often deregulated in pathol. conditions. Our current understanding of how protein kinases and phosphatases orchestrate the phosphorylation changes that control cellular functions has made these enzymes potential drug targets for the treatment of many diseases. The success of the tyrosine kinase inhibitor Gleevec in the treatment of some cancers has further invigorated the development of kinase inhibitors as anti-cancer drugs. A large number of these compds. are currently undergoing clin. trials and there is much expectation on the therapeutic potential of these mols., as more specific and less toxic drugs than currently used generic chemotherapeutic agents. In this manuscript, we review the current status of more than 30 protein kinase inhibitors with proven or potential therapeutic value for cancer treatment. These include inhibitors of receptor and cytosolic tyrosine kinases as well as compds. that target different families of serine/threonine kinases involved in signalling and cell cycle regulation. We also briefly touch on the prospects of phosphatase inhibitors. The combination of kinase inhibitors to target different components of signalling pathways that are found deregulated in tumors is also emerging as an interesting approach for cancer therapy.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:173336 HCAPLUS
DOCUMENT NUMBER: 142:349155
TITLE: Antagonists of activin signaling: mechanisms and

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potential biological applications
AUTHOR(S): Harrison, Craig A.; Gray, Peter C.; Vale, Wylie W.; Robertson, David M.
CORPORATE SOURCE: Prince Henry's Institute of Medical Research, Clayton, VIC 3168, Australia
SOURCE: Trends in Endocrinology and Metabolism (2005), 16(2), 73-78
CODEN: TENME4; ISSN: 1043-2760
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Activins are members of the transforming growth factor-β (TGF-β) superfamily that control many physiol. processes such as cell proliferation and differentiation, immune responses, wound repair and various endocrine activities. Activins elicit these diverse biol. responses by signaling via type I and type II receptor serine kinases. Recent studies have revealed details of the roles of inhibin, betaglycan, follistatin and its related protein follistatin-related gene (FLRG), Cripto and BAMBI in antagonizing activin action, and exogenous antagonists against the activin type I (SB-431542 and SB-505124) and type II (activin-M108A) receptors have been developed. Understanding how activin signaling is controlled extracellularly is the first step in providing treatment for wound healing and for disorders such as cachexia and cancer, which result from a deregulated activin pathway.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1056855 HCAPLUS
DOCUMENT NUMBER: 142:20992
TITLE: Somatic alterations in the human cancer genome
AUTHOR(S): Weir, Barbara; Zhao, Xiaojun; Meyerson, Matthew
CORPORATE SOURCE: Department of Medical Oncology Dana-Farber Cancer Institute Department of Pathology, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Cancer Cell (2004), 6(5), 433-438
CODEN: CCAECI; ISSN: 1535-6108
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Most human malignancies are caused by somatic alterations within the cancer genome, leading to oncogene activation or tumor suppressor gene inactivation. The sequence of the human genome has enabled systematic approaches to identify cancer genome alterations, including point mutations, copy number increases and decreases, loss of allelic heterozygosity, and chromosome translocations. Systematic cancer genome anal. has recently led to the discovery of somatic mutations in the BRAF, PIK3CA, and EGFR genes, among others. With further development of targeted cancer therapies and improvement in genome anal. technol., genome-wide surveys of cancer will likely become tools for diagnosis as well as discovery.
REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:601444 HCAPLUS
DOCUMENT NUMBER: 137:346346

Updated Search

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TITLE: The other side of TGF-β superfamily signal regulation: thinking outside the cell
AUTHOR(S): Gumienny, Tina L.; Padgett, Richard W.
CORPORATE SOURCE: Dept Molecular Biology and Biochemistry, Waksman Institute and Cancer Institute of New Jersey, Rutgers University, Piscataway, NJ, 08854-8020, USA
SOURCE: Trends in Endocrinology and Metabolism (2002), 13(7), 295-299
CODEN: TENME4; ISSN: 1043-2760
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The transforming growth factor β (TGF-β) superfamily of paracrine and autocrine signaling mols. regulates a vast array of developmental and homeostatic processes and is itself exquisitely regulated. The misregulation of these mols. often results in cancer and other diseases. Here, we focus on new research that explores how TGF-β superfamily signaling is controlled between the secreting cell and the target cell. Regulation can occur upon ligand secretion (in a latent protein complex) and in the creation of signaling gradients. Proteins in the extracellular milieu sequester ligand away from or facilitate ligand binding to receptor serine kinases. Ligands even pos. regulate their own neg. regulators. Studies of how TGF-β signaling is regulated extracellularly have broadened our understanding of TGF-β pathways, and could provide clues to our understanding and treatment of diseases resulting from misregulation of these pathways. Many processes depend on TGF-β-mediated signaling, but what controls TGF-βs before they reach target cells. Here, we review the mols. and mechanisms that affect the transport of TGF-β superfamily members to receptors.
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:767906 HCAPLUS
DOCUMENT NUMBER: 132:91484
TITLE: Modulation of cellular apoptotic potential: contributions to oncogenesis
AUTHOR(S): Stambolic, Vuk; Mak, Tak W.; Woodgett, James R.
CORPORATE SOURCE: Amgen Institute, Toronto, ON, M5G 2C1, Can.
SOURCE: Oncogene (1999), 18(45), 6094-6103
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with .apprx.141 refs. The importance of apoptosis as a natural means to eliminate unwanted or damaged cells has been realized over the past decade. Many components required to exercise programmed cell death have been identified and shown to pre-exist in most, if not all, cells. Such ubiquity requires that apoptosis be tightly controlled and suggests the propensity of cells to trigger the cellular death machinery can be regulated. Recently, several signaling pathways have been demonstrated to impact the apoptotic potential of cells, most notably the phosphatidylinositol 3' kinase (PI3'K) pathway. The 3' phosphorylated lipid products generated by this enzyme promote activation of a protein-serine kinase, PKB/AKT, which is necessary and sufficient to confer cell PI3'K-dependent survival signals. The relevance of this pathway to human cancer was revealed by the recent finding that the product of the PTEN tumor suppressor gene acts to

antagonize PI3'K. This review focuses on the regulation and mechanisms by which PKB activation protects cells and the oncol. consequences of dysregulation of the pathway.

REFERENCE COUNT: 141 THERE ARE 141 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:591044 HCAPLUS
DOCUMENT NUMBER: 132:120587
TITLE: STAT signaling in the pathogenesis and treatment of cancer
AUTHOR(S): Frank, David A.
CORPORATE SOURCE: Department of Adult Oncology, Dana-Farber Cancer Institute, Departments of Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA
SOURCE: Molecular Medicine (New York) (1999), 5(7), 432-456
CODEN: MOMEF3; ISSN: 1076-1551
PUBLISHER: Springer-Verlag New York Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 245 refs. Exceptional advances have been made recently in our understanding of the signaling pathways that control cellular growth, differentiation, and survival. These processes are regulated by extracellular stimuli such as cytokines, cell-cell interactions, and cell-matrix interactions, which trigger a series of intracellular events culminating in the modulation of specific genes. STATs are a highly homologous group of transcription factors that are activated by various pathways and regulate many of the genes controlling cellular function. STATs are activated by tyrosine phosphorylation and modulated by serine phosphorylation, placing them at a convergence point for numerous intracellular signaling pathways. Given the importance of STATs in the control of normal physiol. processes, it is not surprising that inappropriate activation of these proteins has been found in human malignancies. A number of distinct mechanisms have been elucidated by which STATs are activated inappropriately, including autocrine or paracrine stimulation of normal receptors and increased activity of tyrosine kinases through enhanced expression, mutations, or the presence of activating proteins. Furthermore, inappropriate STAT serine phosphorylation has been found in several tumors as well. The increased understanding of signaling pathways in tumors can be translated into therapeutic strategies that have the potential to be more selective and less toxic than current anti-cancer treatments. Approaches which may be effective include the development of antagonists of receptors that can trigger STAT activation, inhibitors of the tyrosine and serine kinases that phosphorylate and activate STATs, agents that decrease STAT levels or inhibit their recruitment to kinases, and mols. that can prevent the binding of STATs to target DNA sequences. Thus, elucidation of cellular and biochem. processes in tumors has enhanced our understanding of the pathogenesis of malignancies and may provide the basis for significant advances in therapy.

REFERENCE COUNT: 245 THERE ARE 245 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:322601 HCAPLUS
DOCUMENT NUMBER: 127:874
TITLE: TGF-β signaling through the Smad pathway

10554187

AUTHOR(S): Massague, Joan; Hata, Akiko; Liu, Fang
CORPORATE SOURCE: Howard Hughes Med. Inst., Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA
SOURCE: Trends in Cell Biology (1997), 7(5), 187-192
CODEN: TCBIEK; ISSN: 0962-8924
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 46 refs. Transforming growth factor β (TGF-β) and related cytokines regulate cell fate by signaling through two receptor serine kinases that act in sequence. Signaling by these receptors is mediated by the recently identified Smad protein family. Upon phosphorylation by activated receptors, Smads form complexes, move into the nucleus, associate with DNA-binding proteins and activate gene transcription. Responses mediated by Smads include crucial morphogenic events during fly and frog development as well as cell-cycle arrest in mammalian cells. Furthermore, Smads that mediate growth-inhibitory responses are tumor suppressors mutated in cancer. This review describes how the discovery of the Smad family lets us, for the first time, trace a signaling pathway from TGF-β receptors to target genes.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 20:23:12 ON 21 NOV 2007)

FILE 'HCAPLUS' ENTERED AT 20:23:21 ON 21 NOV 2007
L1 750 S SERINE () KINASE?
L2 54 S L1 AND ISOFORM?
L3 25 S L2 AND INHIBITOR?
L4 1 S L3 AND OVARIAN () CANCER?
L5 1 S L1 AND OVARIAN () CANCER?
L6 55 S L1 AND CANCER?
L7 8 S L6 AND REVIEW/DT

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9 THREONIN
314708 KINASE?
L8 4 THREONIN (W) KINASE?

=> s threonine () kinase?
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449 THREONINES
61867 THREONINE
(THREONINE OR THREONINES)
314708 KINASE?
L9 5788 THREONINE (W) KINASE?

=> s l9 () inhibitor?
1070314 INHIBITOR?
L10 221 L9 (W) INHIBITOR?

=> s l10 and review/dt
2088780 REVIEW/DT
L11 12 L10 AND REVIEW/DT

=> d l11, ibib abs hitstr, 1-12

Updated Search

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L11 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:914201 HCAPLUS
DOCUMENT NUMBER: 147:439276
TITLE: Kinase inhibitors for cancer
AUTHOR(S): Mortlock, A. A.; Barker, A. J.
CORPORATE SOURCE: AstraZeneca, Macclesfield, UK
SOURCE: Comprehensive Medicinal Chemistry II (2006), Volume 7, 183-220. Editor(s): Taylor, John B.; Triggle, David J. Elsevier Ltd.: Oxford, UK.
CODEN: 69JQHZ; ISBN: 978-0-08-044513-7
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review. The first kinase inhibitors have established themselves along side existing agents in the treatment of many cancers. This position has only been reached through a huge global investment by scientists and clinicians, companies, and research institutes, and has challenged the way in which novel anticancer drugs are developed. The search for novel protein kinase inhibitors may constitute more than half of the current medicinal chemical effort in oncol. The lives of millions of current and future cancer patients will be touched by the ability of medicinal chemists, and their partners in drug discovery, to learn lessons from the compds. described in this review. Future progress in the field requires exploitation of the burgeoning structural and bioinformatic data, the conquering of drug-induced resistance, and the opening up of novel inhibitory paradigms, outside the ATP-binding site of active kinases.
REFERENCE COUNT: 459 THERE ARE 459 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:943830 HCAPLUS
DOCUMENT NUMBER: 146:265434
TITLE: New paradigms in anticancer therapy: targeting multiple signaling pathways with kinase inhibitors
AUTHOR(S): Faivre, Sandrine; Djelloul, Siham; Raymond, Eric
CORPORATE SOURCE: Department of Medical Oncology, Hopital Beaujon, Clichy, Fr.
SOURCE: Seminars in Oncology (2006), 33(4), 407-420
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Signal transduction in cancer cells is a sophisticated process that involves receptor tyrosine kinases (RTKs) that eventually trigger multiple cytoplasmic kinases, which are often serine/threonine kinases. A number of tumor models have identified several key cellular signaling pathways that work independently, in parallel, and/or through interconnections to promote cancer development. Three major signaling pathways that have been identified as playing important roles in cancer include the phosphatidylinositol-3-kinase (PI3K)/AKT, protein kinase C (PKC) family, and mitogen-activated protein kinase (MAPK)/Ras signaling cascades. In clin. trials, highly selective or specific blocking of only one of the kinases involved in these signaling pathways has been associated with limited or sporadic responses. Improved understanding of the complexity of signal transduction processes and their roles in cancer has suggested that simultaneous inhibition of several key kinases at the level of receptors and/or downstream serine/threonine kinases may help to optimize the overall therapeutic benefit associated with molecularly targeted

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anticancer agents. Using targeted agents to inhibit multiple signaling pathways has emerged as a new paradigm for anticancer treatment based on preclin. and clin. data showing potent anti-tumor activity of single drugs inhibiting multiple mol. targets or combination therapies involving multiple drugs with selective or narrow target specificity. Preclin. and clin. studies point to mols. on vascular endothelial cells and pericytes as being important targets for anticancer therapies, as well as mols. on or within tumor cells themselves. This suggests that optimal therapeutic approaches to cancer may involve targeting multiple mols. found in both the tumor and supportive tissues. In this review, the authors will use the most recent preclin. and clin. data to describe this emerging paradigm for anticancer therapy involving targeting multiple signaling pathways with tyrosine or serine/threonine kinase inhibitors.

REFERENCE COUNT: 134 THERE ARE 134 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:534551 HCAPLUS
DOCUMENT NUMBER: 143:108800
TITLE: Anti-angiogenesis by inhibition of protein kinase signaling
AUTHOR(S): Teicher, Beverley A.
CORPORATE SOURCE: Genzyme Corporation, Framingham, MA, USA
SOURCE: Cancer Therapy (2005), 221-245. Editor(s): Weber, Georg F. Horizon Bioscience: Wymondham, UK. CODEN: 69GXTJ; ISBN: 1-904933-11-4
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review. Small mol. anti-tumor kinase inhibitors directed toward targets on malignant cells and/or vascular cells have antiangiogenic activity. Kinase inhibitors such as those directed toward EGFR, Her2/neu, BCR-ABL, c-KIT, PKC, Raf and PI3, are antiangiogenic by virtue of blocking secretion of angiogenic factors by affected malignant cells. Kinase inhibitors such as those directed toward VEGFR2, VEGFR1, PDGFR, PKC, Raf and PI3, are antiangiogenic by effects on vascular cells. Those mols. that are having success in the clinic are likely inhibiting a spectrum of kinases important to the function of cell involved in the malignant disease process. While mutations in some kinase genes are well-recognized in the field, recent data indicate that mutations in kinase genes may be more widespread and frequent than previously understood. These mutations may lead to amino acid substitutions in the kinase proteins that alter sensitivity to inhibitors and may enhance selection of patients for specific therapeutics. Small mol. kinase inhibitors are proving useful as antiangiogenic/anti-tumor agents in the clinic. It is likely that kinase inhibitors represent only the first 'targeted' enzyme inhibitors that be useful in the treatment of cancer.
REFERENCE COUNT: 232 THERE ARE 232 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:275033 HCAPLUS
DOCUMENT NUMBER: 143:70751
TITLE: Use of animal models to evaluate signal transduction inhibitors as modulators of cytotoxic therapy
AUTHOR(S): Teicher, Beverly A.
CORPORATE SOURCE: Oncology Portfolio, Genzyme Corporation, Framingham,

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MA, USA
SOURCE: Combination Cancer Therapy (2005), 231-275.
Editor(s): Schwartz, Gary K. Humana Press Inc.: Totowa, N. J.
CODEN: 69GRY6; ISBN: 1-58829-200-2
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review describes signal-transduction inhibitors, such as receptor tyrosine kinases and protein serine-threonine kinase inhibitors, as modulators of cytotoxic therapy.
REFERENCE COUNT: 280 THERE ARE 280 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:506589 HCAPLUS
DOCUMENT NUMBER: 141:98885
TITLE: The development of phosphatidylinositol ether lipid analogues as inhibitors of the serine/threonine kinase, Akt
AUTHOR(S): Gills, Joell J.; Dennis, Phillip A.
CORPORATE SOURCE: NCI, Bethesda, MD, 20889, USA
SOURCE: Expert Opinion on Investigational Drugs (2004), 13(7), 787-797
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The serine/threonine kinase Akt is a component of the phosphatidylinositol 3'-kinase/Akt signal transduction pathway that is activated by receptor tyrosine kinases, activated Ras and integrins. As Akt regulates many processes crucial to carcinogenesis, and Akt activation has been observed in human cancers, intense efforts are underway to develop Akt inhibitors as cancer therapeutics. Towards this aim, phosphatidylinositol ether lipid analogs (PIAs), which are structurally similar to the products of phosphatidylinositol 3'-kinase, have been synthesized. PIAs inhibit Akt translocation, phosphorylation and kinase activity. Furthermore, they selectively induce apoptosis in cancer cell lines that depend on Akt for survival. This review will trace the development of PIAs, cover the biol. activities of PIAs and discuss future steps and challenges in their development.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:436699 HCAPLUS
DOCUMENT NUMBER: 140:399175
TITLE: The design of drug candidate molecules as selective inhibitors of therapeutically relevant protein kinases
AUTHOR(S): Fischer, P. M.
CORPORATE SOURCE: Cyclacel Limited, Dundee, DD1 5JJ, UK
SOURCE: Current Medicinal Chemistry (2004), 11(12), 1563-1583
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The human genome encompasses some 2000 proteins that utilize ATP in one way or another and some 500 of these are protein-tyrosine and protein-serine/threonine kinases (PTKs & PSTKs). Substrate

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phosphorylation by these enzymes is nature's predominant mol. way of organizing cellular signal transduction and regulating biochem. processes in general. It is not surprising, therefore, that abnormal phosphorylation of cellular proteins is a hallmark of disease and that there was a growing interest in the use of kinase inhibitors as drugs. In fact the search for such agents has recently culminated in the approval of the 1st kinase inhibitor drugs for medical use. Although it was demonstrated exhaustively that potent and structurally diverse ATP-antagonistic small mol. kinase inhibitors can be found through mass screening and structure-guided design, the question of biochem., cellular, and in vivo selectivity of such inhibitors remains much less clear. Here the medicinal chemical of kinase inhibitors is reviewed critically with particular emphasis on target selectivity and specificity. Approaches based on chemical genomics, combinatorial target-guided ligand assembly, computational chemical, and structural biol. techniques, which aim at classifying both inhibitors and kinase targets, are given special emphasis. The various strategies in which differences in biochem. mechanism of kinase function can be exploited to attain selective inhibition are also discussed. Furthermore, recent developments in the design of inhibitors to selected individual validated therapeutic kinase targets, including cell cycle kinases and receptor PTKs, etc. are summarized.

REFERENCE COUNT: 239 THERE ARE 239 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:216626 HCAPLUS
DOCUMENT NUMBER: 140:367905
TITLE: Inhibition of Hsp90: a new strategy for inhibiting protein kinases
AUTHOR(S): Sreedhar, Amere Subbarao; Soti, Csaba; Csermely, Peter
CORPORATE SOURCE: Department of Medical Chemistry, Semmelweis University Medical School, Budapest, H-1444 8, Hung.
SOURCE: Biochimica et Biophysica Acta, Proteins and Proteomics (2004), 1697(1-2), 233-242
CODEN: BBAPBW; ISSN: 1570-9639
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The 90-kDa heat shock protein (Hsp90) is a ubiquitous, evolutionarily highly conserved, mol. chaperone in the eukaryotic cytosol. Hsp90, together with a number of other chaperones, promotes the conformational maturation of a large variety of protein kinases. Inhibition of Hsp90 function results in the collapse of the metastable conformation of most of these kinases and leads to their proteolytic elimination by the proteasome. Numerous natural and synthetic Hsp90 inhibitors have been developed in recent years. Some of these inhibitors are also involved in sensitizing tumor cells to pro-apoptotic insults, hence serve as anticancer drugs. Here the authors review these novel protein kinase inhibitors and their emerging role in various cellular processes, apart from their inhibition of Hsp90 protein function. The authors focus not only on Hsp90-tumor progression, but also on cytoarchitecture, as the higher levels of cellular organization need constant remodeling, where the role of Hsp90 requires investigation. The last major aspect deals with protein oxidation, since several Hsp90 inhibitors exert pro-oxidant effects.

REFERENCE COUNT: 132 THERE ARE 132 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

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L11 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:967039 HCAPLUS
DOCUMENT NUMBER: 140:228208
TITLE: Will mTOR inhibitors make it as cancer drugs?
AUTHOR(S): Sawyers, Charles L.
CORPORATE SOURCE: Howard Hughes Medical Institute, University of California, Los Angeles, CA, 90095, USA
SOURCE: Cancer Cell (2003), 4(5), 343-348
CODEN: CCAECI; ISSN: 1535-6108
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review discusses the potential utility of serine/threonine kinase mammalian target of rapamycin (mTOR) inhibitors as anticancer agents. The rationale and clin. details of the empiric approach and the molecularly driven approach for the clin. development of mTOR inhibitors are described.
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:412290 HCAPLUS
DOCUMENT NUMBER: 133:173724
TITLE: G-protein coupled receptor kinases and their inhibitors
AUTHOR(S): Kassack, Matthias U.
CORPORATE SOURCE: Pharmaceutical Institute, University of Bonn, Bonn, 53121, Germany
SOURCE: Expert Opinion on Therapeutic Patents (2000), 10(6), 917-928
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 74 refs. G-protein coupled receptors (GPCRs) are regulated by several processes. One is the phosphorylation by G-protein coupled receptor kinases (GRKs) linked to processes like receptor desensitization, internalisation and downregulation. GRKs also seem to be involved in various processes such as opioid addiction and cardiovascular diseases. So far, no specific and potent inhibitors of GRKs are available except some polyanionic compds. like heparin. A rational approach for a search for inhibitors based on a homologous mol. model of GRK2 revealed disulfonic acid analogs of suramin (NF503 and NF062) as lead compds. for inhibitors of GRK2 (IC50 values of 14 and 25 μM, resp.). GRK2 is extensively expressed in the CNS and therefore, mainly considered responsible for the regulation of GPCRs. So far, no therapeutic patents for inhibition of GRKs are available. Nevertheless, a broad range of serine/threonine kinase inhibitors are reported in the patent literature. An overview of these mainly N-heterocyclic or amino group containing compds. is given in this review. Furthermore, other approaches to inhibit GRKs such as the use of antibodies, antisense oligonucleotides, or adenoviral mediated gene delivery of a peptide inhibitor of GRK2 are presented. Screening against various GRKs is likely to yield new lead compds. to further evaluate a (patho)physiol. role of GRKs. Possible therapeutic applications of GRK inhibitors are discussed.
REFERENCE COUNT: 99 THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS

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L11 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:397279 HCAPLUS
DOCUMENT NUMBER: 131:179174
TITLE: Antisense oligonucleotide inhibition of serine/threonine kinases: an innovative approach to cancer treatment
AUTHOR(S): Cho-Chung, Yoon S.
CORPORATE SOURCE: Cellular Biochemistry Section, Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892-1750, USA
SOURCE: Pharmacology & Therapeutics (1999), 82(2-3), 437-449
CODEN: PHTHDT; ISSN: 0163-7258
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with many refs. The identification of genes that confer a growth advantage on neoplastic cells and the understanding of the genetic mechanism(s) responsible for their activation have made possible a direct genetic approach to cancer treatment using nucleic acid therapeutics. Moreover, the ability to block the expression of individual genes that promote carcinogenesis provides a powerful tool to explore the mol. basis of normal growth regulation, as well as the opportunity for therapeutic intervention. One technique for turning off a single activated gene is the use of antisense oligodeoxynucleotides and their analogs for inhibition of gene expression. The serine/threonine kinases are involved in mediating intracellular responses to external signals, such as growth factors, hormones, and neurotransmitters, and are involved in cell proliferation and oncogenesis. Described herein are recent studies supporting the potential use of oligonucleotides targeting these kinases as chemotherapeutic agents for cancer treatment. The serine/threonine kinases included here are protein kinase A, protein kinase C, and c-raf-1 kinase.
REFERENCE COUNT: 97 THERE ARE 97 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:798525 HCAPLUS
DOCUMENT NUMBER: 130:148115
TITLE: Tyrosine kinase inhibitors in cancer treatment (part II)
AUTHOR(S): Traxler, Peter
CORPORATE SOURCE: Novartis Pharmaceuticals, Therapeutic Area Oncology, Novartis Limited, Basel, CH-4002, Switz.
SOURCE: Expert Opinion on Therapeutic Patents (1998), 8(12), 1599-1625
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 169 refs. In the last few years, enormous progress in the field of signal transduction inhibition has been made. Many companies have entered the field. Along with the epidermal growth factor receptor (EGFR) tyrosine kinase, many other tyrosine kinases have been identified as interesting targets for drug discovery projects. X-ray data of more than 40 crystal structures of protein kinases, in most cases complexed with an inhibitor, have been published. Pharmacophore models for the

binding of inhibitors in the ATP-binding site of protein kinases have been developed that are generally applicable, enabling the rational design of tyrosine as well as serine/threonine kinase inhibitors. It has been proven by numerous examples that the ATP-binding of protein kinases is an exciting target for the design of anticancer drugs. In many cases, it has also been demonstrated that through rational design it is possible to modify a lead structure in such a way that inhibitors with an altered selectivity profile are obtained. Chemical optimization of several lead structures led to development candidates with potent in vitro and in vivo activity fulfilling the pharmacodynamic, pharmacokinetic, toxicol. and tech. (synthesis, formulation) requirements for a clin. candidate. Currently, there are seven tyrosine kinase inhibitors in early phases of clin. trials. In addition, several candidates are close to entering Phase I trials this year or at the beginning of next year. It is expected that pos. results from clin. trials will greatly contribute to the clin. proof of concept of the value of signal transduction inhibition and will greatly stimulate further research in this area. This review is a continuation of a review with the same title of last year and summarizes published patent literature and related publications between 1997 and Sept. 1998.

REFERENCE COUNT: 162 THERE ARE 162 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:980861 HCAPLUS
DOCUMENT NUMBER: 124:24389
TITLE: Inhibitors of serine/threonine kinases
AUTHOR(S): Lee, John C.; Adams, Jerry L.
CORPORATE SOURCE: SmithKline Beecham Pharm., King of Prussia, USA
SOURCE: Current Opinion in Biotechnology (1995), 6(6), 657-61
CODEN: CUOBE3; ISSN: 0958-1669
PUBLISHER: Current Biology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 35 refs. Several serine/threonine kinase inhibitors have been described recently that are sufficiently selective, and therefore useful as biochem. probes, for studying the role of kinases in signaling pathways. In addition, these newer classes of kinase inhibitor may well provide an impetus for the development of drugs to attenuate certain cellular responses in the treatment of diseases. Importantly, within the past yr, specific and potent inhibitors have been reported for both the new mitogen-activated protein (MAP) kinase homolog CSBP and MAP kinase kinase-1.

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=> s akt () inhibitor?
         14797 AKT
            26 AKTS
         14810 AKT
                 (AKT OR AKTS)
       1070314 INHIBITOR?
L12         331 AKT (W) INHIBITOR?

=> s l12 and cancer?
        354501 CANCER?
L13         128 L12 AND CANCER?

=> s l13 and review/dt
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L14 9 L13 AND REVIEW/DT

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L14 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:1205746 HCAPLUS
DOCUMENT NUMBER: 147:419140
TITLE: Recent progress in the development of ATP-competitive and allosteric Akt kinase inhibitors
AUTHOR(S): Lindsley, Craig W.; Barnett, Stanley F.; Yaroschak, Melissa; Bilodeau, Mark T.; Layton, Mark E.
CORPORATE SOURCE: VICB Program in Drug Discovery, Department of Pharmacology, Vanderbilt Medical Center, Department of Chemistry, Vanderbilt University, Nashville, TN, 37232, USA
SOURCE: Current Topics in Medicinal Chemistry (Sharjah, United Arab Emirates) (2007), 7(14), 1349-1363
CODEN: CTMCCL; ISSN: 1568-0266
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. This article describes recent advances in the development and biol. evaluation of small mol. inhibitors for the serine/threonine kinase Akt (PKB). Akt plays a pivotal role in cell survival and proliferation through a number of downstream effectors. Recent studies indicate that unregulated activation of the PI3K/Akt pathway is a prominent feature of many human cancers and Akt is over-expressed or activated in all major cancers. Akt is considered an attractive target for cancer therapy and inhibition of Akt alone or in combination with standard cancer chemotherapeutics has been postulated to reduce the apoptotic threshold and preferentially kill cancer cells. The development of specific and potent inhibitors will allow this hypothesis to be tested in animals. Recently, several series of small mol., ATP-competitive inhibitors have been reported with a range of Akt potencies and selectivities. Phosphatidylinositol (PI) analogs have been reported to inhibit Akt, but these inhibitors may also have specificity problems with respect to other pleckstrin homol. (PH) domain containing proteins and may have poor bioavailability. In addition, novel allosteric inhibitors have been reported which are PH domain dependent, exhibit selectivity for the individual Akt isoenzymes and inhibit the activity and the activation of Akt. Compds. within these classes Akt inhibitors have sufficient potency and specificity to test for tumor efficacy in animal models and recently reported preliminary expts. are reviewed.

L14 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:1103606 HCAPLUS
DOCUMENT NUMBER: 147:397590
TITLE: Recent progress in the discovery of Akt inhibitors as anticancer agents
AUTHOR(S): Li, Qun
CORPORATE SOURCE: Libertyville, IL, 60048, USA
SOURCE: Expert Opinion on Therapeutic Patents (2007), 17(9), 1077-1130
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

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AB A review. Akt, also referred to as protein kinase B (PKB) or Related to A and C (RAC), is one of the major direct downstream targets of phosphoinositide 3-kinase (PI3K). As it plays a central role in promoting cancer cell proliferation and survival through a growing list of key substrates, intense efforts are underway to find inhibitors of Akt for the treatment of cancer. Discovery of potent and novel inhibitors of Akt has been facilitated greatly by the availability of the x-ray structure of the active form of Akt and by its structural similarity with other serine/threonine kinases. In this review, new Akt inhibitors for the treatment of cancer are comprehensively reviewed, with emphasis on small mol. inhibitors that bind to the ATP-binding site, allosteric sites and the PH domains. Inhibitors of pseudosubstrates and antisense oligonucleotides, as well as Akt inhibitors with unknown mechanism of actions, are also reviewed. Results of clin. trials of several Akt drug candidates are briefly discussed. A brief summary of Akt structure and regulation and the evidences supporting Akt as a cancer target is provided as well. The patent literature is surveyed through July 2007.

L14 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:617275 HCAPLUS
DOCUMENT NUMBER: 147:397651
TITLE: Targeting the PI3K-Akt pathway in kidney cancer
AUTHOR(S): Park, Jin-Young; Lin, Pei-yin; Weiss, Robert H.
CORPORATE SOURCE: Division of Nephrology, Department of Internal Medicine, Immunology Graduate Group, University of California, Davis, CA, 95616, USA
SOURCE: Expert Review of Anticancer Therapy (2007), 7(6), 863-870
CODEN: ERATBJ; ISSN: 1473-7140
PUBLISHER: Future Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Kidney cancer, or renal cell carcinoma, is a relatively rare malignancy but is metastatic at diagnosis in a third of patients; metastatic disease has a dismal prognosis. Conventional chemotherapy has been woefully inadequate, thus novel targets for 'designer' therapies are being actively evaluated. The PI3K-Akt signaling cascade, owing to its dual role in both survival and mitogenic signaling, is in theory an ideal therapeutic target for this disease, but may also represent its fatal flaw. Thus, largely due to toxicity issues, no PI3K or Akt inhibitors are currently ready for clin. application. In this review, we discuss PI3K-Akt inhibitors as well as inhibitors of pathways and targets both immediately up- and downstream of this cascade, many of which show promise in the clinic.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:479444 HCAPLUS
DOCUMENT NUMBER: 147:462
TITLE: Inhibitors of Akt Activity
AUTHOR(S): Lippa, Blaise
CORPORATE SOURCE: Discovery Chemistry, Pfizer, Inc. PGRD Groton, Groton, CT, 06340, USA
SOURCE: Expert Opinion on Therapeutic Patents (2007), 17(5), 577-581

Updated Search

CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Imidazo[4,5-c]pyridine analogs with Akt (PKB) kinase antagonist activity are claimed. The compds. contain a 4-amino-1,2,5-oxadiazole substituent at the 2-position of the ring system with an alkyne substituent at the 4-position, and diverse functionality at the 6-position. The compds. are indicated to be useful in the treatment of cancer and arthritis.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:350627 HCAPLUS
DOCUMENT NUMBER: 144:465166
TITLE: Akt Signaling and Cancer: Surviving but not Moving On
AUTHOR(S): Toker, Alex; Yoeli-Lerner, Merav
CORPORATE SOURCE: Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
SOURCE: Cancer Research (2006), 66(8), 3963-3966
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The frequent deregulation of the phosphoinositide 3-kinase/Akt survival signaling pathway in cancer has prompted significant interest in blocking this pathway to treat cancer. Recently, however, two studies have shown that the Akt isoform Akt1 limits the invasive migration of breast cancer cells. These studies suggest that Akt1 may have a dual role in tumorigenesis, acting not only pro-oncogenically by suppressing apoptosis but also anti-oncogenically by suppressing invasion and metastasis. We discuss the possible implications of these findings for therapeutic development of Akt inhibitors to treat cancer.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1349832 HCAPLUS
DOCUMENT NUMBER: 144:307393
TITLE: Molecular strategies targeting the host component of cancer to enhance tumor response to radiation therapy
AUTHOR(S): Kim, Dong Wook; Huamani, Jessica; Fu, Allie; Hallahan, Dennis E.
CORPORATE SOURCE: Department of Radiation Oncology, Vanderbilt Ingram Cancer Center, Nashville, TN, USA
SOURCE: International Journal of Radiation Oncology, Biology, Physics (2005), Volume Date 2006, 64(1), 38-46
CODEN: IOBPD3; ISSN: 0360-3016
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The tumor microenvironment, in particular, the tumor vasculature, as an important target for the cytotoxic effects of radiation therapy is an established paradigm for cancer therapy. The authors review the evidence that the phosphoinositide 3-kinase (PI3K)/Akt

pathway is activated in endothelial cells exposed to ionizing radiation (IR) and is a mol. target for the development of novel radiation sensitizing agents. On the basis of this premise, several promising preclin. studies that targeted the inhibition of the PI3K/Akt activation as a potential method of sensitizing the tumor vasculature to the cytotoxic effects of IR have been conducted. An innovative strategy to guide cytotoxic therapy in tumors treated with radiation and PI3K/Akt inhibitors is presented. The evidence supports a need for further investigation of combined-modality therapy that involves radiation therapy and inhibitors of PI3K/Akt pathway as a promising strategy for improving the treatment of patients with cancer.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1211155 HCAPLUS
DOCUMENT NUMBER: 144:16324
TITLE: The Akt/PKB pathway: molecular target for cancer drug discovery
AUTHOR(S): Cheng, Jin Q.; Lindsley, Craig W.; Cheng, George Z.; Yang, Hua; Nicosia, Santo V.
CORPORATE SOURCE: Departments of Pathology and Interdisciplinary Oncology, H Lee Moffitt Cancer Center and Research Institute, University of South Florida College of Medicine, Tampa, FL, 33612, USA
SOURCE: Oncogene (2005), 24(50), 7482-7492
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The serine/threonine kinase Akt/PKB pathway presents an exciting new target for mol. therapeutics, as it functions as a cardinal nodal point for transducing extracellular (growth factor and insulin) and intracellular (receptor tyrosine kinases, Ras and Src) oncogenic signals. In addition, alterations of the Akt pathway have been detected in a number of human malignancies. Ectopic expression of Akt, especially constitutively activated Akt, is sufficient to induce oncogenic transformation of cells and tumor formation in transgenic mice as well as chemoresistance. Akt has a wide range of downstream targets that regulate tumor-associated cell processes such as cell growth, cell cycle progression, survival, migration, epithelial-mesenchymal transition and angiogenesis. Blockage of Akt signaling results in apoptosis and growth inhibition of tumor cells with elevated Akt. The observed dependence of certain tumors on Akt signaling for survival and growth has wide implications for cancer therapy, offering the potential for preferential tumor cell killing. In the last several years, through combinatorial chemical, high-throughput and virtual screening, and traditional medicinal chemical, a number of inhibitors of the Akt pathway have been identified. This review focuses on ongoing translational efforts to therapeutically target the Akt pathway.

REFERENCE COUNT: 131 THERE ARE 131 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:506589 HCAPLUS
DOCUMENT NUMBER: 141:98885
TITLE: The development of phosphatidylinositol ether lipid analogues as inhibitors of the serine/threonine

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kinase, Akt
AUTHOR(S): Gills, Joell J.; Dennis, Phillip A.
CORPORATE SOURCE: NCI, Bethesda, MD, 20889, USA
SOURCE: Expert Opinion on Investigational Drugs (2004), 13(7), 787-797
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The serine/threonine kinase Akt is a component of the phosphatidylinositol 3'-kinase/Akt signal transduction pathway that is activated by receptor tyrosine kinases, activated Ras and integrins. As Akt regulates many processes crucial to carcinogenesis, and Akt activation has been observed in human cancers, intense efforts are underway to develop Akt inhibitors as cancer therapeutics. Towards this aim, phosphatidylinositol ether lipid analogs (PIAs), which are structurally similar to the products of phosphatidylinositol 3'-kinase, have been synthesized. PIAs inhibit Akt translocation, phosphorylation and kinase activity. Furthermore, they selectively induce apoptosis in cancer cell lines that depend on Akt for survival. This review will trace the development of PIAs, cover the biol. activities of PIAs and discuss future steps and challenges in their development.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:607171 HCAPLUS
DOCUMENT NUMBER: 138:162768
TITLE: Targeting serine/threonine protein kinase B/Akt and cell-cycle checkpoint kinases for treating cancer
AUTHOR(S): Li, Qun; Zhu, Gui-Dong
CORPORATE SOURCE: Cancer Research, Global Pharmaceutical Discovery, Abbott Laboratories, Abbott Park, IL, 60064-6101, USA
SOURCE: Current Topics in Medicinal Chemistry (Hilversum, Netherlands) (2002), 2(9), 939-971
CODEN: CTMCCL; ISSN: 1568-0266
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Over the past decade, protein kinases have emerged as a group of mol. targets with the potential to be "cancer-specific", allowing the selective targeting of cancer cells vs. normal cells. These selective anticancer drugs would eliminate the cytotoxic side effects that are associated with conventional cancer chemotherapy. This article will focus on two emerging and less-explored protein serine/threonine kinase targets: PKB/Akt and checkpoint kinase 1 (Chk1). Protein kinase B/Akts are a group of serine/threonine kinases that are overexpressed in a variety of human tumors. An Akt inhibitor would target the imbalance of pro-vs. anti-apoptosis regulation in cancerous as compared to healthy cells. Thus, a greater therapeutic window than conventional cytotoxic chemotherapy is expected. Cell-cycle checkpoints have become attractive targets since some of them, such as the G1/S checkpoint, are defective in most tumor cells. Inhibition of one or more of the remaining checkpoint(s) could make cancerous cells more sensitive than healthy cells toward DNA damaging agents or radiation therapy. Among the checkpoint kinases, Chk1 appears to be an attractive mol. target. Chk1 blocks the activation

of the Cdc2-cyclin B kinase complex, and hence entry into mitosis, by disrupting the translocation of the phosphatase Cdc25C from the cytoplasm to the nucleus. A limited number of small mol. inhibitors in this emerging field and their mode of action will be reviewed.

REFERENCE COUNT: 275 THERE ARE 275 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT